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Role of Routine Bone Marrow Trephine Biopsy and Flow Cytometry in Patients With Marginal Zone Lymphoma − a Comparative Analysis and Clinical Implications

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Background: There are three variants of marginal zone lymphoma (MZ): nodal, extranodal and splenic. The most common sites of extranodal involvement include the orbit, stomach, salivary glands and thyroid. A recent study suggested no differences in relapse rate and survival between patients who did or did not undergo routine staging bone marrow (BM) biopsy (1). The role of routine BM examination in all patients with marginal zone lymphoma (MZL) remains to be determined, especially in those with radiologically early stage (I/II) stage extranodal MZL. Few studies have compared BM trephine histological biopsy (BMB) findings with results of flow cytometry (FC) analysis. We aim to (1) determine if routine BM examination is required in all patients with radiologically limited stage MZL and (2) to determine the concordance rate between the two methods of BM examination.
Methods: We retrospectively analyzed the incidence of BM involvement by trephine biopsy (BMB) and FC analysis in 182 patients with MZL.
Results: Majority of patients with MZL presented with early stage disease (139/182). Of the 182 patients, the incidence of BM involvement (either BMB + or FC +) was 10% (19/198). Among patients with radiologically stage 1 or 2 disease, the incidence of BM involvement was 0.8% (1/127), 14.3% (1/7) and 60% (3/5) for extra-nodal, nodal and splenic MZL, respectively. Among the 127 patients with radiological early stage extranodal MZL, BM involvement was detected in only one patient with stage II orbital MZL and none of the patients with other extranodal sites of involvement (gastric, 0/44; thyroid, 0/15, others, 0/31). On univariate analysis, factors predicting for BM marrow involvement (BMB+ or FC+) in patients with radiologically early stage MZL include Haemoglobin (Hb) level <10 g/dL ($p = 0.017$), elevated Lactate dehydogenase level or LDH ($P = 0.014$) and presence of non-extranodal MZL($P < 0.001$). Of the 182 patients, 98 patients, a concurrent FC analysis on BM was available. Concordance between the two methods (trephine biopsy and flow cytometry) was detected in 95% of the cases (12% BMB+/FC+; 85% BMB−/FC−). In 5 cases, the results were discrepant (1 BMB+/FC−; 4 BMB−/FC+).
Conclusion: BM involvement in patients with radiological early stage extranodal MZL is low (0.8%). Our findings suggest that BM biopsy may be safely omitted in majority of patients with radiologically early stage extranodal MZL, particularly those with stage I disease. However, BM is essential in patients with nodal or splenic MZL. It should also be considered in radiologically early stage patients with low Hb or elevated LDH. The concordance rate between FC and BMB is 95%.

References

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Lymphoblastic T-cell Lymphoma/leukemia – the Impact of Age-related Immunophenotype to Clinical Presentation and Biologic Behavior

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Background: T-cell lymphoblastic lymphoma (T-LBL) and leukemia (T-ALL) are distinct clinical presentations of related malignant diseases that arise in developing thymocytes. The clinical distinction between T-LBL and T-ALL is based on the extent of tumour cell dissemination within the bone marrow and peripheral blood. Investigations into the molecular prognostic factors of T-LBL derive from T-ALL. The risk stratification is still difficult by the lack of well stablished prognostic factors, especially concerning T-LBL. Furthermore, T-LBL biopsies are often classified histologically only, without phenotyping. Immature phenotypes have been associated with poor prognosis predominantly occuring in adults but not pediatric cases. We analyzed the impact of age, clinical and immunophenotype features on treatment response and survival of T-LBL/T-ALL.
Material and Methods: Patients with T-LBL ($n = 48$) and T-ALL ($n = 42$) diagnosed at the Instituto Nacional de Câncer, Brazil from 1997 to 2009 were classified according to the WHO 2008 classification. The immunophenotype of T-cells from bone marrow, peripheral blood and tissue micro-array biopsy material was based on the results of flow cytometry and immunohistochemical staining. The maturational stages of T-LBL and T-ALL were analysed regarding to age-groups and survival.
Results: The median age was 15.5 years (range 1−60 years) and there was a male predominance. Concerning the immunophenotypic profile, the cortical phenotype predominated (T-LBL, 62%; T-ALL, 65%) with tendency for difference between age-groups (childhood versus adult patients, $p = 0.07$) in T-LBL. Non-cortical phenotype increased with age among T-LBL cases. The CD34 was expressed in 5% of T-LBL and 28% of T-ALL cases ($p = 0.01$). Cortical phenotype confered a better survival for T-ALL ($p = 0.07$), but not for T-LBL ($p = 0.38$). The 5-year overall survival rate was 52% for both clinical forms, but comparatively a higher rate of initial failure was observed in T-LBL. Treatment response was the only prognostic factor identified in T-LBL patients.
Conclusions: Although the survival rates were similar, the events related to death were not the same for T-LBL and T-ALL. The clinical presentations of T-LBL and T-ALL are similar in many aspects, however it remains unknown whether there might be additional differences distinguishing T-LBL from T-ALL.
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Effective WT1 Peptide Vaccination With Long-lasting Amplification of WT1-specific Cytotoxic T Lymphocytes in a Patient With CML in Chronic Phase

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Background: Cytotoxic T lymphocytes (CTLs) are presumed to kill the relevant antigen-expressing tumour cells including leukemic stem cells which display intrinsic resistance against tyrosine kinase inhibitors such as imatinib in CML patients. In order to clarify the safety and effectiveness of WT1 peptide vaccination for the patients with CML, we started WT1 peptide vaccination in combination with imatinib therapy for a patient with CML.
Materials and Methods: A 51 years-old male with CML in CP had been treated with 400 mg imatinib for 4 years. bcr-abl transcripts decreased transiently but gradually increased to more than 1,000 copies thereafter. HLA-A*2402-restricted 9mer WT1 peptides (CYTWNQMNL; a.a. 235–243), which had been identified to possess an anti-tumour immunogenicity, were administered subcutaneously at the dose of 1 mg/day every 2 weeks in combination with 400 mg imatinib for first 5 months and thereafter every 4 weeks for 12 months. The vaccination was undertaken 22 times totally. The appearance of WT1-specific CTLs in PB was confirmed by evaluating the frequency of MHC/WT1 tetramer$^+$CD8$^+$ T cells by using mixed lymphocyte peptide culture (MLPC).
Results: Although bcr-abl transcripts increased up to more than 2,000 copies after the the initiation of WT1 vaccination every 2 weeks, the transcripts have decreased to less than 500 copies by the administration of WT1 peptides every 4 weeks. After seven months from the cessation of WT1 peptide vaccination bcr-abl transcripts decreased to the level of major molecular response (MMR), which is lasting thereafter for 18 months. While WT1-specific CTLs were not detected in PB before WT1 peptide vaccination, the CTLs appeared after the second vaccination and remained at the level of nearly 15/10^6 CD8$^+$ cells thereafter. In addition, for over 25 months after the cessation of vaccine therapy the WT1 specific CTLs have remained to be detected with a remarkable decrement of bcr-abl transcripts during the period. The MHC/WT1 tetramer$^+$ cells showed cytotoxicity against only leukemia cells expressing WT1 and HLA-A*2402.
Conclusions: The present study showed that WT1 peptide vaccination for an imatinib-pretreated CML patient is feasible and effective, which is due to the long-lasting amplification of WT1-specific CTLs with cytotoxicity against WT1-expressing leukemia cells.

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Psychosocial Effect and Evaluation of the Health-related Quality of Life in Patients With Non-Hodgkin Lymphoma

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Backround: The aim of this study was to record the impact of non-Hodgkin lymphoma (NHL) on the psychological health and health-related quality of life (HRQOL) of patients suffering from NHL.
Material and Method: We studied 23 outpatients suffering from well-controlled, uncomplicated NHL who had the ability to sustain a regular job. We tried to record the psychosocial effects resulting of NHL and to evaluate their HRQOL, comparing them to 23 healthy controls with similar demographic characteristics. To the patients and controls were given the Short-Form Healthy Syrvey (SF-36) and a questionnaire based on the Hamilton and Marker's depression scales.